**ORTEC INTERNATIONAL, INC**
**Audubon Business & Technology Center**
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Confidential

# Orcel™

**Composite Cultured Skin (CCS)**

## Instructions for Use

## For Managing Donor Sites in Burn Patients

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# Composite Cultured Skin (CCS)
# Instructions for Use

**CAUTION:** Federal Law restricts this device to sale by or on the order of a physician**.**

## 1. INDICATIONS FOR USE

Composite Cultured Skin is indicated for use in accelerating wound closure of split thickness donor site wounds in burn patients.

## 2. PRODUCT DESCRIPTION

Composite Cultured Skin is composed of a collagen matrix in which allogeneic human skin cells, (i.e., epidermal keratinocytes and dermal fibroblasts) are cultured in two distinct layers. The collagen cross-linked sponge consists primarily of Type I bovine collagen laminated on one side with a thin gel layer of acid-soluble bovine collagen.

The device is manufactured under aseptic conditions from human neonatal male foreskin tissue. The donor's mother is tested and found to be negative for syphilis and for human viruses, including HTLV I&II, Hepatitis B&C, HIV 1&2, EBV and HHV-6. The donor's fibroblast and keratinocyte cells are tested for human viruses (and found to be negative for HTLV I&II, Hepatitis B, HIV 1&2, EBV, and HHV-6), retroviruses, bacteria, fungi, yeast, mycoplasma, karyology, isoenzymes, tumorigenicity, normal growth and morphology. The final product is tested for morphology, cell viability, sterility, mycoplasma, and physical container integrity. Product manufacture also includes animal-derived reagents, which are tested and found to be negative for viruses, retroviruses, bacteria, fungi, yeast, and mycoplasma before use and all bovine material is obtained from countries free of Bovine Spongiform Encephalopathy (BSE). The device measures approximately 6 cm x 6 cm (minimally 36 $cm^2$).

## 3. CONTRAINDICATIONS

- Composite Cultured Skin is contraindicated for use on clinically infected wounds (see Precautions).
- Composite Cultured Skin is contraindicated in patients with known allergies to bovine collagen.

## 4. WARNINGS

- Allergic reactions to bovine collagen have been reported. Since bovine collagen is a component of Composite Cultured Skin, discontinue product use if a patient shows evidence of an immune reaction.

## 5. PRECAUTIONS

***Caution:*** Composite Cultured Skin may contain trace amounts of penicillin, streptomycin, gentamicin, and fungizone (amphotericin B) used during cell processing. Avoid the use of this product in patients known to be allergic to these materials.

***Caution:*** Allergic reactions to the components (see Section 8) of the shipping medium could occur. Patients should notify their physician of any symptoms of an allergic reaction. In clinical studies evaluating over 186 patients, no allergic reactions to the shipping medium were reported.

***Caution:*** Composite Cultured Skin should be stored in its shipping container until ready for use.

***Caution:*** Do not use cytotoxic agents with Composite Cultured Skin. Device exposure to mafenide acetate, silver sulfadiazine, polymyxin/nystatin, Providone-iodine solution or Dakin's Solution may also reduce Composite Cultured Skin's viability.

***Caution:*** If clinical signs of infection (pain, edema, erythema, drainage, odor, warmth, and/or unexplained fever) are present or develop, do not apply Composite Cultured Skin until the infection is adequately treated and eradicated. All infections should be evaluated and treated according to standard clinical practice.

***Caution:*** Composite Cultured Skin should be handled using aseptic technique and placed on a prepared wound bed, free of necrotic debris, within 30 minutes of removing sterile tray from sealed pouch.

***Caution:*** **DO NOT OPEN AND DO NOT USE** Composite Cultured Skin after the expiration date.

***Caution:*** **DO NOT USE** Composite Cultured Skin if sterile package is opened or damaged.

***Caution:*** **DO NOT** reuse, freeze, refrigerate, or sterilize after opening.

## 6. ADVERSE EVENTS

There were 12 mild to moderate adverse events involving the CCS treated donor sites and 13 mild to moderate adverse events involving the control treated donor sites. The events for each treatment, the severity of the event and its frequency are presented in Table 6.1.

## Table 6.1: Adverse Events Reported With Donor Site Involvement

| | CCS (N=82) | | | | | | Biobrane-L (N=82) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mild-Mod | | Severe | | Life-Threatening | | Mild-Mod | | Severe | | Life-Threatening | |
| **Adverse Event** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| Blisters | 0 | - | 0 | - | 0 | - | 1 | 1.2 | 0 | - | 0 | - |
| Tenderness to palpation | 1 | 1.2 | 0 | - | 0 | - | 0 | - | 0 | - | 0 | - |
| Pain | 4 | 4.9 | 0 | - | 0 | - | 4 | 4.9 | 0 | - | 0 | - |
| Infection | 1 | 1.2 | 0 | - | 0 | - | 1 | 1.2 | 0 | - | 0 | - |
| Itching at Both Donor Sites | 1 | 1.2 | 0 | - | 0 | - | 1 | 1.2 | 0 | - | 0 | - |
| Bullous Eruption | 0 | 0.0 | 0 | - | 0 | - | 1 | 1.2 | 0 | - | 0 | - |
| Pruritus | 4 | 4.9 | 0 | - | 0 | - | 5 | 6.1 | 0 | - | 0 | - |
| Rash Pustular | 1 | 1.2 | 0 | - | 0 | - | 0 | 0.0 | 0 | - | 0 | - |

None of the patients undergoing re-cropping (01-009, 03-004, 08-005) experienced adverse events at the re-cropped sites. All adverse events reported for these patients occurred before re-cropping and were not associated with donor sites. These events are listed with other non-site related events in Table 6.2.

Table 6.2 lists all adverse events without donor site involvement, stratified by severity categories and presented in decreasing order of frequency (life threatening, severe, mild-moderate).

## Table 6.2: Adverse Events Without Donor Site Involvement

| | Mild-Mod | | Severe | | Life-Threatening to Fatal | | Uncategorized Severity | |
|---|---|---|---|---|---|---|---|---|
| **Adverse Event** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| Dyspnoea | | | 3 | 3.7 | 1 | 1.2 | | |
| Anaemia | 11 | 13.4 | 1 | 1.2 | | | | |
| Vomiting | 9 | 11.0 | 1 | 1.2 | | | | |
| Nausea | 8 | 9.8 | 1 | 1.2 | | | | |
| Hyperglycaemia | 5 | 6.1 | 1 | 1.2 | | | | |
| Rehabilitation NEC | 3 | 3.7 | 1 | 1.2 | | | | |
| Scar (not donor site) | 2 | 2.4 | 1 | 1.2 | | | | |
| Sepsis | 2 | 2.4 | 1 | 1.2 | 2 | 2.4 | | |
| Skin Malformation (not donor site) | 2 | 2.4 | 1 | 1.2 | | | | |
| Hypothermia | 1 | 1.2 | 1 | 1.2 | | | | |
| Pneumonia | 1 | 1.2 | 1 | 1.2 | | | | |
| Achalasia Cardiae | | | 1 | 1.2 | | | | |
| Dystonia | | | 1 | 1.2 | | | | |
| Entropion/Ectrop Rep Nec | | | 1 | 1.2 | | | | |
| Other Pleural Incision | | | 1 | 1.2 | | | | |
| Constipation | 16 | 19.5 | | | | | | |
| Insomnia | 12 | 14.6 | | | | | | |
| Fever | 8 | 9.8 | | | | | | |
| Pharyngitis | 8 | 9.8 | | | | | | |
| Pruritus | 8 | 9.8 | | | | | | |
| Agitation | 6 | 7.3 | | | | | | |
| Anxiety | 5 | 6.1 | | | | | | |
| Atelectasis | 5 | 6.1 | | | | | | |

## Table 6.2: Adverse Events Without Donor Site Involvement

| | Mild-Mod | | Severe | | Life-Threatening to Fatal | | Uncategorized Severity | |
|---|---|---|---|---|---|---|---|---|
| **Adverse Event** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| Hypernatraemia | 5 | 6.1 | | | | | | |
| Relaxation Of Scar (not donor site) | 5 | 6.1 | | | | | | |
| Thrombocythaemia | 5 | 6.1 | | | | | | |
| Vaginal Haemorrhage (Females: N=19) | 1 | 5.3 | | | | | | |
| Diarrhoea | 4 | 4.9 | | | | | | |
| Dyspepsia | 4 | 4.9 | | | | | | |
| Infection (Not Donor Site) | 4 | 4.9 | | | | | | |
| Depression | 3 | 3.7 | | | | | | |
| Hypokalaemia | 3 | 3.7 | | | | | | |
| Oedema (not donor site) | 3 | 3.7 | | | | | | |
| Other Local Destruc Skin (not donor site) | 3 | 3.7 | | | | | | |
| Pulmonary Infiltration | 3 | 3.7 | | | | | | |
| Thrombocytopenia | 3 | 3.7 | | | | | | |
| Anorexia | 2 | 2.4 | | | | | | |
| Bilirubinaemia | 2 | 2.4 | | | | | | |
| Bone Development Abnormal | 2 | 2.4 | | | | | | |
| Brain Stem Disorder | 2 | 2.4 | | | | | | |
| Confusion | 2 | 2.4 | | | | | | |
| Convulsions | 2 | 2.4 | | | | | | |
| Dizziness | 2 | 2.4 | | | | | | |
| Finger Amputation (not donor site) | 2 | 2.4 | | | | | | |
| Headache | 2 | 2.4 | | | | | | |
| Healing Impaired | 2 | 2.4 | | | | | | |
| Hyperchloraemia | 2 | 2.4 | | | | | | |
| Hyperkalaemia | 2 | 2.4 | | | | | | |
| Hypertension Aggravated | 2 | 2.4 | | | | | | |
| Hypotension | 2 | 2.4 | | | 1 | 1.2 | | |
| Leukocytosis | 2 | 2.4 | | | | | | |
| Pain (not donor site) | 2 | 2.4 | | | | | | |
| Pleural Effusion | 2 | 2.4 | | | | | | |
| Pneumothorax | 2 | 2.4 | | | | | | |
| Pulmonary Congestion | 2 | 2.4 | | | | | | |
| Sinusitis | 2 | 2.4 | | | | | | |
| Skin Repair & Plasty NEC (not donor site) | 2 | 2.4 | | | | | | |
| Skin Suture NEC (not donor site) | 2 | 2.4 | | | | | | |
| Surgical Intervention | 2 | 2.4 | | | | | | |
| Urinary Tract Infection | 2 | 2.4 | | | | | 1 | 1.2 |
| Vascular Disorder (not donor site) | 2 | 2.4 | | | | | | |
| Vein Disorder (not donor site) | 2 | 2.4 | | | | | | |
| Abdominal Pain | 1 | 1.2 | | | | | | |
| A/G Ratio Abnormal | 1 | 1.2 | | | | | | |
| Aspiration | 1 | 1.2 | | | | | | |

## Table 6.2: Adverse Events Without Donor Site Involvement

| | Mild-Mod | | Severe | | Life-Threatening to Fatal | | Uncategorized Severity | |
|---|---|---|---|---|---|---|---|---|
| **Adverse Event** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| Back Pain | 1 | 1.2 | | | | | | |
| Cellulitis (not donor site) | 1 | 1.2 | | | | | | |
| Collagenosis (not donor site) | 1 | 1.2 | | | | | | |
| Coughing | 1 | 1.2 | | | | | | |
| Crying Abnormal | 1 | 1.2 | | | | | | |
| Dehydration | 1 | 1.2 | | | | | | |
| Dermatitis Fungal (not donor site) | 1 | 1.2 | | | | | | |
| Dysphagia | 1 | 1.2 | | | | | | |
| Dysphonia | 1 | 1.2 | | | | | | |
| Dysuria | 1 | 1.2 | | | | | | |
| Ectropion | 1 | 1.2 | | | | | | |
| Ext Fix Dev-Metacar/Carp | 1 | 1.2 | | | | | | |
| Eye Abnormality | 1 | 1.2 | | | | | | |
| Fibrillation Ventricular | 1 | 1.2 | | | | | | |
| Full-Thick Skin Graft NEC (not donor site) | 1 | 1.2 | | | | | | |
| Gout | 1 | 1.2 | | | | | | |
| Haematoma | 1 | 1.2 | | | | | | |
| Haemoptysis | 1 | 1.2 | | | | | | |
| Haemorrhoids | 1 | 1.2 | | | | | | |
| Hernia Inguinal | 1 | 1.2 | | | | | | |
| Heterograft To Skin (not donor site) | 1 | 1.2 | | | | | | |
| Hyperlipaemia | 1 | 1.2 | | | | | | |
| Hypermagnesaemia | 1 | 1.2 | | | | | | |
| Hyperphosphataemia | 1 | 1.2 | | | | | | |
| Hyperreflexia | 1 | 1.2 | | | | | | |
| Hypertension | 1 | 1.2 | | | | | | |
| Hypoaesthesia | 1 | 1.2 | | | | | | |
| Hypocalcaemia | 1 | 1.2 | | | | | | |
| Hypochloraemia | 1 | 1.2 | | | | | | |
| Hypoglycaemia | 1 | 1.2 | | | | | | |
| Hypophosphataemia | 1 | 1.2 | | | | | | |
| Hypoxia | 1 | 1.2 | | | | | | |
| Infection Aggravated (Not Donor Site) | 1 | 1.2 | | | | | | |
| Leucopenia | 1 | 1.2 | | | | | | |
| Lid Reconst W Skin Graft | 1 | 1.2 | | | | | | |
| Lid Reconstr W Graft Nec | 1 | 1.2 | | | | | | |
| Lymphoedema | 1 | 1.2 | | | | | | |
| Medication Error (not donor site) | 1 | 1.2 | | | | | | |
| Mitral Insufficiency | 1 | 1.2 | | | | | | |
| Muscle Contractions Involuntary | 1 | 1.2 | | | | | | |
| Myalgia | 1 | 1.2 | | | | | | |
| Neoplasm NOS | 1 | 1.2 | | | | | | |
| Neuropathy | 1 | 1.2 | | | | | | |
| Neuropathy Peripheral | 1 | 1.2 | | | | | | |
| Paralysis | 1 | 1.2 | | | | | | |

**Table 6.2: Adverse Events Without Donor Site Involvement**

| | Mild-Mod | | Severe | | Life-Threatening to Fatal | | Uncategorized Severity | |
|---|---|---|---|---|---|---|---|---|
| **Adverse Event** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| Pulmonary Collapse | 1 | 1.2 | | | | | | |
| Pulmonary Oedema | 1 | 1.2 | | | | | | |
| Rash (not donor site) | 1 | 1.2 | | | | | | |
| Remove Impltd Device NOS (not donor site) | 1 | 1.2 | | | | | | |
| Renal Failure Acute | 1 | 1.2 | | | | | | |
| Respiratory Insufficiency | 1 | 1.2 | | | | | | |
| Rotator Cuff Repair | 1 | 1.2 | | | | | | |
| Stridor | 1 | 1.2 | | | | | | |
| Stupor | 1 | 1.2 | | | | | | |
| Sweating Increased | 1 | 1.2 | | | | | | |
| Tachycardia | 1 | 1.2 | | | | | | |
| Tachycardia Ventricular | 1 | 1.2 | | | | | | |
| Thrombophlebitis Deep | 1 | 1.2 | | | | | | |
| Tooth Ache | 1 | 1.2 | | | | | | |
| Tot Nasal Reconstruction | 1 | 1.2 | | | | | | |
| Urinary Retention | 1 | 1.2 | | | | | | |
| Cardiac Arrest | | | | | 1 | 1.2 | | |
| Larynx Oedema | | | | | 1 | 1.2 | | |
| Multiple Organ Failure | | | | | 1 | 1.2 | | |

The coded preferred term of "dyspnoea" included four patients, two of which had verbatim events reported as "ARDS" (patients 01-008 and 15-009). Both of these patients had predisposing respiratory conditions in their medical histories prior to study start. The outcome of the ARDS events in both patients was death, unrelated to study device.

### Deaths

Three patients died during the study. None of the deaths were considered related to the study treatment. Two of these patients were the ARDS patients mentioned above. The third, patient 15-007, had an adverse event of bacterial sepsis resulting in death.

## 7. CLINICAL EXPERIENCE

Two studies were conducted in the management of donor sites in patients requiring split thickness skin autografting for the management of burn injuries. One study was a pilot study and was followed by the main study. Both studies were prospective, open, randomized and controlled. They were matched-pairs design (i.e., each patient had two designated donor sites of equivalent surface area) and each site was randomized to receive a single application of either CCS or a control dressing. Patients were followed through post-treatment Day 28.

In the pilot study, the Kaplan-Meier estimates of the percent of healing from both computerized planimetric analysis and the investigators' assessments showed at least 50% of the eight patients were healed by Day 12 with CCS treatment and by day 25 with the control dressing. There was a statistically significantly ($p=0.034$) shorter healing time observed with CCS than with the control dressing. At each time point, the mean

percentages of CCS donor site healing were larger than the mean percentages for the control dressing, and at Days 14 and 21, these differences were statistically significant (p=0.014 and 0.026, respectively).

The main study was conducted at 12 clinical sites and included 82 patients. The mean and median times to 100% wound healing by photographic, planimetric, and investigator assessments were all significantly shorter (p=0.05) for CCS treated sites compared to the control dressing. Photographic assessment yielded mean healing times of 18.0 and 22.4 days for CCS and the control dressing, respectively and median times of 15 and 22 days for CCS and the control dressing, respectively.

CCS treatment resulted in significantly better scar outcome at weeks 12 and 24 compared to the control dressing as measured by the Vancouver and Hamilton Scar Scores.

In both studies, CCS was well tolerated. In the pilot study, all eight patients had at least one adverse event. All serious adverse events were considered by the Investigator to be unlikely related to study treatment and there were no statistically significant differences between CCS and the control dressing for donor site pain or itching at any of the study time points. In the pivotal study, all donor-site-related adverse events were mild to moderate in severity and there were no reports of serious adverse events associated with either CCS or control dressing treatment. Clinically meaningful differences in favor of CCS were observed for signs of infection, signs of site breakdown and site pain severity scores.

**Immune Response:**

Investigations in the United States, to date, have not revealed any significant clinical manifestations of product-related immune reactions. Sera drawn from patients in U.S. studies revealed no antibody responses to ***bovine Type I collagen***. Impact of device application on patients' humoral and cellular immune responses to the allogeneic human cellular components of CCS, i.e., keratinocytes and fibroblasts, such as HLA antigens or potential blood group antigens, has not yet been evaluated.

## 8. HOW SUPPLIED

### A. Package Description

Composite Cultured Skin (CCS) measures approximately 6 cm x 6 cm (minimally 36 $cm^2$). A non-adherent, medical grade mesh (N-Terface® (Winfield Laboratories, Inc., Dallas, Texas)) is placed on both aspects of the device to protect the cells. One sheet is blue N-Terface®, which covers the fibroblast/dermal side of Composite Cultured Skin. The other sheet is white N-Terface®, which protects the keratinocyte/epidermal surface of Composite Cultured Skin. The device is packaged in a plastic tray with protein-free packaging medium containing HEPES buffered DMEM, L-Glutamine and MEM non-essential amino acids to maintain cell viability during storage and shipping.

The plastic tray is sealed within a peelable inner pouch to provide a sterile barrier against moisture and gas. The inner pouch is, in turn, sealed inside a heavier-gauge outer pouch that protects the inner pouch sterile barrier and the product against damage during shipment. The multi-stage packaged product is packed with pre-chilled gel packs and

shipped to the destination in a padded and insulated shipping container that maintains a temperature of 11-19° C (for up to 72 hr.).

To maintain cell viability, Composite Cultured Skin is aseptically manufactured, but not terminally sterilized. CCS is shipped following a preliminary 48 hour incubation sterility test to confirm the absence of microbial growth. Final (14 day incubation) sterility test results are not available at the time of device application.

## B. Storage

1. Composite Cultured Skin is to be stored in the original shipping container in which it was received. Do not store in refrigerator or freezer. The original shipping container maintains the correct storage temperature of 11 to 19°C.

2. Do not remove from original shipping container until ready to use.

## C. Package Inspection

1. Visually inspect the Composite Cultured Skin clear packaging. The clear packaging should be intact. If the packaging is damaged, the Composite Cultured Skin device is not acceptable for patient application.
2. Visually inspect the medium in which the Composite Cultured Skin device is transported. The medium should not appear cloudy in color. Any cloudiness of the medium is an indicator the Composite Cultured Skin device is not acceptable for patient application.
3. Visually inspect packaging label. Check expiration date and time. Adhere strictly to expiration date and time guidelines.

## 9. DIRECTIONS FOR USE

### A. Method of Application

**General**

1. Prepare the wound bed so that it is clean and free of necrotic material.
2. Open outer clear package of the Composite Cultured Skin device containing inner sterile pouch.
3. Dispense inner sterile pouch containing plastic tray onto the sterile field. Open pouch.
4. Place the tray on a sterile flat surface with the blue N-Terface® backing dermal side facing up.
5. To open the tray, stabilize the bottom tab while simultaneously lifting up on the top tab.
6. Using sterile noncrushing forceps, gently remove and discard the blue N-Terface® backing material.
7. With two sterile noncrushing forceps, grasp adjacent corners of the device in unison with the white N-Terface® backing material.
8. Position the device so that the white N-Terface® backing material (covering the epidermal surface) is facing up and away from the cleaned wound bed. Leave white N-Terface® in place to serve as the primary contact layer.
9. In this orientation, the dermal aspect of the device is in direct contact with the wound bed.
10. See specific indications for use below for further directions regarding outer dressings.

**Donor Sites**

1. The Composite Cultured Skin (CCS) device should be positioned so that there is a slight overlap (approximately 0.5 cm) onto intact skin. If more than one device is used to cover a wound surface, a slight overlapping of the edges of each Composite Cultured Skin device is recommended. Once placed on the wound bed, further manipulation of the Composite Cultured Skin device to improve positioning should be minimized, although it may be performed, as long as the device is grasped together with the white backing in place and moved in unison.
2. Cover the CCS device(s) with a nonadherent dressing and outer gauze wrap.
3. Allow overlying dressings to remain undisturbed for approximately 48 to 72 hours and then follow post application directions for care.

### B. Post Application Directions of Care

**Donor Sites**

1. After Composite Cultured Skin has been applied to the affected areas as instructed in the directions for use, the donor site should be inspected by removing overlying nonadherent dressings at a minimum of every 48 to 72 hours.

   **Note: The white N-Terface® backing lying directly on top of the Composite Cultured Skin should remain in place for 1 week.**

2. The site should be inspected for any signs of redness, tenderness, itching, pain, or foul odor. The surrounding area may be gently cleansed with normal saline.
3. The site should be redressed with nonadherent dressings and an overlying gauze wrap.
4. After 1 week, the dressings should be removed and an attempt to gently peel back the white backing with forceps should be made.

   **NOTE: The white backing may be adherent and may require soaking the area with normal saline to encourage loosening of the backing material. If portions of the backing remain adherent despite soaking, leave in place for approximately 24 to 48 hours and reattempt.**

5. Once the white backing has been completely removed, gently cleanse the area with normal saline. If there are portions of the wound that remain unhealed, cover with nonadherent dressings and wrap with an overlying gauze wrap. Continue to assess healing of the area on a 24- to 48-hour basis.
6. Once the area has healed, caution should be taken so as to prevent any unnecessary trauma to the newly healed area, as newly healed skin may be fragile and susceptible to wound breakdown. Patients are instructed to care for the newly healed skin as directed by their physicians.
7. Patients are instructed to inspect the newly healed area daily for any of the following signs of breakdown: redness, tenderness, blistering, foul odor, drainage, or a moist, glistening appearance of the area. If any of these signs appear, the patient should notify their physician.

## 10. PATIENT INFORMATION

Patients and parents should be counseled regarding the following information:

1. Basic information about patient's condition,
2. Basic information about Composite Cultured Skin,
3. How Composite Cultured Skin is used in the treatment of donor sites, and
4. Post-operative care.

## 11. PEEL OFF LABEL

Remove the peel-off label from the CCS package label and place it in the patient's chart. This label bears the lot number and expiration date of the CCS.

**Manufactured By:** Ortec International, Inc.
3960 Broadway
New York, NY 10032

**For more information, call (212) 740-6999.**

**In the case of an emergency, call pager number 1(800) 501-3554.**

**Date of Issuance: Month XX, 200X [insert date of approved labeling]**